REMARKS

In the outstanding Office action, claims 1, 3 to 7, 9 to 28 and 30 to 32 were presented for examination. Claims 1, 3 to 7, 9 to 28 and 30 to 32 were rejected.

In this amendment, applicant has amended claims 1, 9, 10, 12 to 15, 19, 22 and 27. No claim has been cancelled or added. Accordingly, claims 1, 3-7, 9-28 and 30-32 continue to be pending for examination and, as will be discussed in detail below, the application is believed to be in condition for allowance. Favorable reconsideration of the claims now pending is respectfully requested.

Request for an Interview

In the event that any issue remains outstanding after entry of this amendment, and consideration of the following remarks, applicant respectfully requests the Examiner contact the undersigned to arrange a telephone interview for the purpose of advancing the prosecution of this application.

Claim Amendments

Minor amendments have been made to Claims 1 and 9 to correct informalities.

Claims 10, 12, 15 and 19 have been amended to relate to a process and to depend from process claim 9.

Claim 13 has been amended to depend from claim 1 and to recite that the recombinant or synthetic gelatin-like polypeptide has a molecular weight between 3,000 Dalton and 40,000 Dalton.

Claim 14 has been amended to relate to a process, to depend from claim 9 and to recite that the recombinant or synthetic gelatin-like polypeptide has a molecular weight between 3,000 Dalton and 40,000 Dalton.

Support for the amendments to claims 13 and 14 can be found at page 9, lines 15-18 of applicant's specification.

Double Patenting

Applicant notes the advice on page 10 of the action as to a potential double patenting objection being raised to claims 10, 12, 15 and 19. Claims 10, 12, 15 and 19 have been amended to relate to a process and to depend from process claim 9. Thus, claims 10, 12, 15 and 19 now appear to avoid any possible double patenting objection.

Reply Comments

Applicant appreciates, and has carefully considered, the helpful reply comments appearing at pages 7-9 of the Office action and has the following observations on same.

In <u>Reply (2)</u> the Office action states that: "It is not clear what Applicants' mean by "hydrolyzed" gelatin and "non-hydrolyzed" gelatin (in their remarks of 05.22.09, p.13) since <u>gelatin is</u> hydrolyzed collagen".

Applicant agrees that gelatin is hydrolyzed collagen. Hydrolysis can convert the three helically wound gelatin strands in the collagen molecule into three single strands of gelatin. In addition, gelatin itself also can be hydrolyzed, yielding hydrolyzed gelatin material having a lower average molecular weight than non-hydrolyzed gelatin. Hydrolyzed gelatin is well known in the art.

The distinction between hydrolyzed gelatin and non-hydrolyzed gelatin is made, for example, in Kokil et al "Effect of Molecular Weight of Hydrolyzed Gelatin on its Binding Properties in Tablets" AAPS PharmSciTech 2004; 5(3). See, for example, the Introduction and the first paragraph under Results and Discussion. Hydrolyzed and partially hydrolyzed gelatin, and their uses, are also described in EP 0,781,779, US 4,147,772 and US 4,273,762. These patent documents are referenced on page 2 of applicant's specification. Additional references to hydrolyzed gelatin as a component of vaccines appear at page 61, lines 27-33 of Chang et al. (of record herein.)

Applicant believes that this explanation of the nature of hydrolyzed gelatin shows that the conclusion reached in Reply (1) as to the molecular weight of gelatin being "distinctly lower" than the 140,000 Dalton of instant SEQ ID NO:1 (human Col1A1), is incorrect. 140,000 Dalton is the molecular weight of a single molecule of this gelatin compound. In collagen, three such gelatin molecules are held together in a triple helix conformation by cross-linking, and the collagen molecule has a much higher molecular weight than an individual gelatin molecule. Hydrolyzed gelatins can be fragments of approximately 60 kDa or less. See Chang et al. page 63, lines 38-39.

In further reference to Reply (1), applicant's remarks in the May 2009 amendment regarding the molecular weight limitation in claims 1 and 9 showed that this limitation distinguished claims 1 and 9 from full-length native collagen sequences. Those particular remarks were not intended to be addressed to Chang et al. Claims 1 and 9 are distinguished from Chang et al. by other limitations, including that the stabilizer polypeptide recited in claims 1 and 9 is to have a calculated glass transition temperature that is higher than 180 degrees Celsius.

Claim Objections

Claims 22 and 27 have been amended to overcome the objections. Applicant appreciates the Office having pointed out the deficiencies appearing in claims 22 and 27 before amendment.

Claim Rejections - 35 U.S.C. § 103 Alleged Unpatentability

? In the outstanding Office action, claims 1, 3 to 7, 9 to 28 and 30 to 32 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over International Publication No. WO 01/34801, (Chang et al.), in view of Wang 2000 International Journal of Pharmaceutics 203 (2000) 1-60 (Wang) as evidenced by Cortesi et al. (1998) Biomaterials 19:1641-1649 (Cortesi et al.).

In reply, applicant respectfully submits that claim 1 is unobvious over any combination of Wang with Chang et al., notwithstanding the teachings of Cortesi et al., for reasons which will now be explained.

Applicant's claim 1 claims a vaccine composition and recites that the composition comprises a polypeptide stabilizer which has a particular calculated glass transition temperature, namely a value of higher than 180 degrees Celsius. Claim 1 further recites that the glass transition temperature is <u>calculated using a mathematical formula,</u> and certain amino acid values. Thus, the glass transition temperature will not depend upon analytical conditions but will always be the same for a given embodiment of polypeptide stabilizer.

By employing a mathematical calculation to determine the glass transition temperature, a variety of embodiments of the claimed lyophilized composition can be easily manufactured. For example, a facile selection of a particular amino acid sequence that has an appropriate glass transition temperature to be employed as a polypeptide stabilizer can be made from a longer native sequence. Also, the claimed invention can be practiced without the variations in results, and uncertainties, that can arise with an analytical method employing an experimentally determined glass transition temperature.

Furthermore, applicant has discovered that the stability of a lyophilized composition comprising a recombinant or synthetic gelatin-like polypeptide stabilizer relates to the <u>calculated</u> glass transition temperature of the polypeptide which was not known to the art prior to applicant's invention.

In addition, applicant has provided a recombinant or synthetic gelatin-like polypeptide having the molecular weight and calculated glass transition temperature limitations recited in claim 1, for use in a lyophilized composition, which does not appear to have been known prior to applicant's invention.

The Office action alleges that Chang et al. discloses lyophilized vaccines employing recombinant gelatin as a stabilizer, that the recombinant gelatin should have characteristics similar to an animal-source gelatin, that the recombinant gelatin can be derived from a human sequence or animal source, and that the recombinant gelatin can have a molecular weight range between 0 kDa to 350 kDa, for example 0 to 60 kDa.

Also, the Office action acknowledges that Chang et al. does not teach a glass transition temperature for gelatin.

Further, the Office action alleges that Wang discloses that lyophilized proteins need stabilization in the solid state to survive long-term storage as pharmaceuticals, that the glass transition temperature of protein formulations is one of the major determinants of protein stability, that the higher the glass transition temperature of the polymer in the formulation, the more stable the protein formulation, and that the glass transition temperature therefore may be used as a guiding parameter to screen protein stabilizers.

Still further, the Office action alleges that it is known in the art that mammalian gelatins have a glass transition temperature of 180-200° C, and cites Cortesi et al., p. 1647 as evidence of this allegation.

Based on these findings, the Office action concludes that it would have been obvious to modify the teachings of Chang et al. by producing a lyophilized composition comprising a protein drug and a recombinant gelatin so that the recombinant gelatin has a polypeptide sequence that is identical to a region of a native human collagen sequence having a high glass transition temperature (as suggested by Wang), where the recombinant gelatin has the same functional and/or structural characteristics as the native gelatin, i.e. has a glass transition temperature of 200" C (as evidenced by Cortesi et al.).

Applicant respectfully disagrees with this conclusion believing that a person of ordinary skill in the art would not be motivated to combine Wang with Chang et al. This is because Chang et al. does not teach that Chang et al.'s recombinant gelatin can have characteristics similar to those of a native human collagen sequence. Rather, Chang et al. discloses that their invention provides, in one embodiment, recombinant gelatin with characteristics similar to <u>hydrolyzed</u> animal-source gelatin..." (underlining added). See Chang et al. page 65, lines 21-23 relied upon in the Office action.

Also, Wang does not appear to describe or suggest that a calculated glass transition temperature of a polypeptide would be related to the stability of a lyophilized composition comprising the polypeptide.

Accordingly, claim 1 appears to be unobvious over any combination of Wang with Chang et al., notwithstanding Cortesi et al., and therefore patentable and allowable, for this reason alone.

In addition, the conclusion reached in the Office action as to what a person of ordinary skill in the art would learn from the cited art is less than what applicant has claimed in claim 1 because claim 1 recites that the recombinant or synthetic gelatin-like polypeptide employed as a stabilizer has a calculated glass transition temperature of higher than 180 degrees Celsius (underlining added.)

None of the cited art, not Chang et al., nor Wang, nor Cortesi et al. appears to disclose a recombinant or synthetic gelatin-like polypeptide having a calculated glass transition temperature of higher than 180 degrees Celsius (underlining added.) Nor do any of the references appear to disclose how such a polypeptide can be made.

Accordingly, claim 1 furthermore appears to be unobvious over any combination of Wang with Chang et al., notwithstanding Cortesi et al., and therefore patentable and allowable, for this additional reason.

Applicant's reasoning will now be further explained.

To support the rejection, the Office Action relies upon Cortesi et al. as allegedly disclosing that mammalian gelatins have a glass transition temperature of 180-200° C (page 1647 of Cortesi et al.). This glass transition temperature in Cortesi et al. appears to be an experimentally determined glass transition temperature ("Mammalian gelatins show an intense glass transition temperature . . ."). In contrast, applicant's claim 1 recites a calculated glass transition temperature not an experimentally determined glass transition temperature. Therefore, Cortesi et al. does not appear to disclose this limitation of claim 1.

The Office action does not appear to distinguish between an experimentally determined glass transition temperature and a calculated glass transition temperature. These are different ways of determining the glass transition temperature which may result in different values. Experimentally determined values may be subject to variation whereas calculated values are consistent for a given molecule.

Also, applicant believes that a person of ordinary skill in the art will give the disclosure in Cortesi et al. as to mammalian gelatins having a glass transition temperature of 180-200° C a liberal interpretation. Given the context of this statement, which is that of a discussion of the thermal behavior of native and cross-linked gelatin microspheres, applicant believes the skilled person may understand the statement to refer to the cross-linked gelatin microspheres investigated by Cortesi et al. as much as any other mammalian gelatins.

This conclusion is reached because the language used by Cortesi et al. on page 1647 is rather general, namely "Mammalian gelatins show an intense glass transition temperature located around 180-200° C. . . " (underlining added.) Also, Cortesi et al. shows, in Fig. 7, a differential scanning calorimetry (DSC) curve of an untreated gelatin disk, line a, which appears to show a T_g (glass transition temperature) of about 160° C, i.e. substantially below 180-200° C. Furthermore, in the same paragraph on page 1647, Cortesi et al., describes that uncross-linked gelatin films show a T_g of 170 ± 10° C and quotes an authority for the experimental determination of the value.

Also, Cortesi et al. does not appear to cite any reference to support the statement on page 1647 regarding the mammalian gelatin glass transition temperature. Nor does Cortesi et al. appear to specify a particular mammalian gelatin that has such a glass transition temperature or provide precise conditions under which the cited glass transition temperature of the mammalian gelatins was determined. As Wang explains, on page 28, bottom half of the righthand column of Wang, several factors can affect the determination of a glass transition temperature by DSC. Some factors cited, with references given, include poor reproducibility, limited detectability, formulation heterogeneity, moisture content, and the temperature history of samples. Wang concludes (at the top of page 29) that these factors may partly explain why glass transition temperatures can be so different for the same compound, as reported by different investigators.

Therefore, in the absence of a description of a particular material or of experimental conditions a person of ordinary skill in the art may have questions as to the value, scope or significance of Cortesi et al.'s statement that "Mammalian gelatins show an intense glass transition temperature located around 180-200° C . . ." and may not place great reliance upon it.

In any event, Cortesi et al. does not appear to be pertinent to the patentability of applicant's claim 1 because Cortesi et al. appears to relate to whole gelatins and cross-linked gelatins, not to hydrolyzed gelatins. Therefore, a person of ordinary skill in the art would not be motivated to combine Cortesi et al.'s teaching with that of Chang et al., even in light of Wang teachings regarding the role of glass transition temperature in the stability of lyophilized solid protein pharmaceuticals, because, as already pointed out herein, Chang et al. describes recombinant gelatin "with characteristics similar to those of <u>hydrolyzed</u> animal-source gelatin..." (emphasis added), not animal-source gelatin per se. See Chang et al. page 65, lines 21-23 relied upon in the Office action.

Furthermore, as described in applicant's specification, at page 3, lines 29-31, in general, native collagen polypeptides have a calculated glass transition temperature of about 170° C, or less. Nothing in Cortesi et al., or on the record herein, appears to suggest that the mammalian gelatins referenced in Cortesi et al. will have a <u>calculated</u> glass transition temperature greater than 170° C.

In addition, nothing in Cortesi et al. appears to suggest that Cortesi et al.'s mammalian gelatins that "show an intense glass transition temperature located around 180-200° C" would have a molecular weight between 3,000 Dalton and 80,000 Dalton, as is recited in applicant's claim 1.

Accordingly, the Office action does not appear to show that a person of ordinary skill in the art would have believed that a recombinant or synthetic gelatin-like polypeptide to be employed as a stabilizer in a lyophilized composition should have a calculated glass transition temperature of at least 180° C. Wang appears to relate to isolated, intact gelatins. When

considering Wang's disclosure, at best, a skilled person might be led to screen for known "intact" gelatins having the highest glass transition temperature. In doing so a skilled person apparently would arrive at a gelatin having a calculated glass transition temperature of at most 170° C, since no gelatin having a higher calculated glass transition temperature appears to be known to the art. Wang does not appear to suggest that a person of ordinary skill in the art should look for parts of a gelatin molecule that would have a calculated glass transition temperature of at least 180° C.

Even were a skilled person to be motivated by Wang to screen Chang et al.'s lower molecular weight recombinant gelatin-like molecules for a high <u>calculated</u> glass transition temperature, which Wang does not appear to provide reason to do, the best the skilled person would find apparently would be a value of about 174.1° C for Chang et al.'s SEQ ID NO: 33, which does not meet the limitation in claim 1 of at least 180° C. See applicant's amendments filed September 24, 2008, pp. 16-17 and November 9, 2007, p. 13.

?from May 2009

Applicant respectfully disagrees. Chang et al. has been discussed previously on the record herein. Chang et al. discloses the use of recombinant gelatins (having a large range of molecular weights) as stabilizers in pharmaceutical compositions, in particular in vaccines. Chang et al.'s disclosure is exemplified by gelatins having molecular weights in the range of 5-65 kDa (page 69, Table 2 of Chang et al.).

Still further, as applicant has explained on the record herein, Chang et al. does not disclose a synthetic or recombinant gelatin-like polypeptide having a glass transition temperature higher than 180 degrees Celsius, as is required by applicant's amended claims 1 and 9. And Chang et al. does not disclose or suggest a method of preparing a synthetic or recombinant gelatin-like polypeptide having a glass transition temperature higher than 180 degrees Celsius.

Furthermore, Chang et al. also does not provide knowledge of the relationship between the glass transition temperature and the improved stability of a lyophilized physiological composition

that can be obtained by employing in the lyophilized composition a recombinant or synthetic polypeptide which might suggest to a skilled worker the invention claimed in applicant's claims 1 and 9.

Wang does not appear to correct these deficiencies of Chang et al. as will now be explained. Wang does not appear to provide a clear teaching, or suggestion, to a person of ordinary skill in the art that the stability of a lyophilized composition comprising a physiologically active agent can be improved by employing in the composition a synthetic or recombinant gelatin-like polypeptide having a relatively high glass transition temperature.

Accordingly, Wang does not provide clear guidance or suggestion to a person of ordinary skill in the art that the stability of a lyophilized pharmaceutical composition can be improved by employing a synthetic or recombinant gelatin-like polypeptide having a calculated glass transition temperature higher that 180° C, as defined in applicant's amended claims 1 and 9. Rather the number of stability-related factors identified by Wang and the nature of the discussion of each, would suggest to a person of ordinary skill in the art that controlling the stability of a solid protein pharmaceutical is a complex problem, in applicant's view.

Applicant's invention as now claimed in amended claims 1 and 9 comprises substantially more than is disclosed by any combination of Chang et al. with Wang, and is therefore unobvious and patentable, applicant believes. Neither Chang et al. nor Wang plainly correlates an improved stability of a lyophilized physiological composition with a synthetic or recombinant gelatin-like polypeptide having a relatively high glass transition temperature. Neither Chang et al. nor Wang discloses a synthetic or recombinant gelatin-like polypeptide having a calculated glass transition temperature of higher than 180 degrees Celsius as is recited in applicant's. Neither Chang et al. nor Wang provides a method of preparing a synthetic or recombinant gelatin-like polypeptide having a glass transition temperature of higher than 180 degrees Celsius. And neither Chang et al. nor Wang discloses that the sequence of a native collagen can have a region which has a higher calculated Tg than the calculated Tg of the complete sequence of the native collagen.

Furthermore, Wang does not appear to suggest utilizing a region of a native human collagen sequence having a high glass transition temperature? (D claim?)

Independent Claim 9 relates to a process for lyophilizing a composition and recites comparable limitations to those recited in claim 1. Accordingly, claim 9 appears to be unobvious and therefore allowable over the art of record, for the same reasons as claim 1.

For the above reasons, applicant respectfully submits that claims 1 and 9, are unobvious and patentable over Chang et al. in view of Wang, notwithstanding the disclosure of Cortesi et al., and are therefore allowable. Favorable reconsideration and allowance of amended claims 1 and 9 are respectfully requested.

Dependent Claims

Claims 3-7 and claims 10-28 and 30 depend from claim 1, either directly or indirectly, and claims 31 and 32 depend from claim 9, either directly or indirectly. Dependent claims 3-7, 10-28 and 31-32 therefore incorporate all the limitations of their respective parent claims and therefore are believed to be allowable for at least the same reasons that claims 1 and 9 are believed to be allowable. Furthermore, dependent claims 3-7, 10-28 and 31-32 are believed clearly and patentably distinguished from the art of record, and therefore allowable, by the additional limitations they recite.

For example, claim 24 recites that the complete amino acid sequence of the recombinant or synthetic gelatin-like polypeptide is identical to or essentially similar to a selected region of the amino acid sequence of a native collagen having a calculated average glass transition temperature higher than that of the native collagen by at least 10 degrees Celsius, as recited in claim 24. Claim 30 recites the selection of such a region. None of Chang et al., Wang or Cortesi et al. appears to suggest that such a region even exists.

With regard to claim 24, the Office action appears to suggest that a gelatin molecule could be regarded as a selected region of a collagen molecule. Applicant respectfully does not believe

that a person of ordinary skill in the art would understand "selected region", as used in claim 24, in this sense. Moreover, the Office action does not appear to show how the limitation that the selected region is to have a calculated average glass transition temperature higher than that of the native collagen by at least 10 degrees Celsius, as recited in claim 24, is met by the art of record.

Conclusion

In view of the above amendments and the discussion relating thereto, it is respectfully submitted that the instant application, as amended, is in condition for allowance. Favorable reconsideration and allowance are earnestly solicited. If for any reason the Examiner feels that consultation with applicant's representative would be helpful in the advancement of the prosecution, the Examiner is invited to contact the undersigned practitioner.

Respectfully submitted,

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